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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with o-, m-, p-xylene and mixed xylenes. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1987. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1987. Drinking Water Criteria Document for Xylene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Drinking Water, Washington, DC.

U.S. EPA. 1986a. Health and Environmental Effects Profile for Xylenes (o-, m-, p-). Prepared for the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-86/216. NTIS PB88-246/86/AS.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

For protection against toxicity from inhalation exposure, an RfD_{SI} and RfD_I of 0.3 mg/m³ for o-, m-, p- and mixed xylenes has been estimated for human CNS efects (Hake et al., 1981). The Hake et al. (1981) study identified CNS effects (100 ppm p-xylene) as acute exposure. However, the RfD Workgroup, because of other supporting studies, verified the RfD_I of 0.3 mg/m³ on May 18, 1989.

An RfD_{SO} of 250 mg/day for o-, m-, p- and mixed xylenes was estimated from a NOAEL of 357 mg/kg/day for reduced body weights of rats in a 13-week gavage study (NTP, 1986). An RfD_O of 126 mg/day for o-, m-, p- and mixed xylenes was based on a NOAEL of 180 mg/kg/day for reduced survival in male rats in a 103-week gavage study (NTP, 1986). A CS of 10 was based on the mortality seen at the higher dose, 357 mg/kg/day.

These RfD values should be considered provisional and subject to change as subchronic oral testing sponsored by OSW and OTS is completed.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Services
CNS	Central nervous system
CS	Composite score
EEG	Electroencephalogram
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average
VER	Visual evoked response

1. ENVIRONMENTAL CHEMISTRY AND FATE

Xylene can exist in three isomeric forms. Commercial xylene is a mixture of three isomers in the following percent ranges: o-xylene, 10-25%; m-xylene, 45-70%; and p-xylene, 6-15% (NIOSH, 1975). The relevant physical and chemical properties of the individual xylenes and their environmental fate are as follows:

Chemical class	monocyclic aromatic hydrocarbon
CAS Registry No.	o-xylene, 95-47-6; m-xylene, 108-38-3 p-xylene, 106-42-3
Molecular weight	106.17
Vapor pressure in mm Hg at 20°C	o-xylene, 5; m-xylene, 6; p-xylene, 6.5 (Verschueren, 1983)
Water solubility in mg/ℓ at 25°C	o-xylene, 170.5; m-xylene, 146; p-xylene, 156 (Sutton and Calder, 1975)
Log octanol/water partition coefficient	o-xylene, 3.12; m-xylene, 3.20; p-xylene, 3.15 (U.S. EPA, 1986a)
BCF	o-xylene, 7.3-21.4; m-xylene, 6.4-23.6; p-xylene, 23.6 (U.S. EPA, 1986a)
K_{oc}	o-xylene, 48-68; o-, m- and p-xylene, 350 (estimated) (U.S. EPA, 1986a)
Half-lives in Air:	o-xylene, 13 hours; m-xylene, 8 hours; p-xylene, 15 hours (Singh et al., 1981)
Water:	o-, m- and p-xylene, 1.5-11.0 days (estimated) (U.S. EPA, 1985, 1986a)

The predominant removal mechanism for xylenes in the atmosphere is reaction with photochemically generated hydroxyl radicals. Detection of xylenes in rainwater suggests that small amounts of these compounds may also be removed from the atmosphere by washout (U.S. EPA, 1986a).

The dominant process in the removal of xylenes from water appears to be volatilization (U.S. EPA, 1987). The aquatic half-life (1.5-11.0 days) is the volatilization half-life estimated using an EXAMS model and the data given in U.S. EPA (1986a). Volatilization rates vary depending on the depth of water, temperature, oxygen exchange rate and the amount of organic matter in the sediments (U.S. EPA, 1987).

The half-lives for the three xylenes in soil could not be located in the available literature; however, based upon the characteristics of their evaporation from water, volatilization is expected to be the predominant loss mechanism from the soil surface. In subsurface soil, biodegradation of xylenes is likely to be a slow process (U.S. EPA, 1987). The persistence of xylenes in soils has been reported to be $\geq$6 months (NRC, 1980). Therefore, in subsurface soils with low organic carbon content, xylenes may infiltrate into groundwater from soil. This has been substantiated by the widespread occurrence of xylenes in groundwater (U.S. EPA, 1986a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Although explicit data regarding the absorption of xylenes from the gastrointestinal tract of animals or humans were not located, it can be inferred that absorption by this route is nearly complete. In the rabbit, 85-90% of an administered oral dose of xylene isomers (ranging from 0.9-1.7 g/animal) was accounted for as metabolites in the urine, while pulmonary excretion may have accounted for the remaining xylene (Bray et al., 1949).

2.2. INHALATION

Studies that evaluate the inhalation absorption in humans exposed to doses ranging from 100-1300 mg/m^3 indicated that ~60% (43-74%) of the xylene present in the inspired air, regardless of the isomer or isomer mixture used, is absorbed (Astrand et al., 1978; Riihimaki et al., 1979a; Sedivec and Flek, 1974, 1976; Gamberale et al., 1978; Se'nczuk and Orlowski, 1978). Exercise may increase slightly the relative amount of xylene absorbed (Astrand et al., 1978; Riihimaki et al., 1979b).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Twenty male Long-Evans rats, 12-19 months old and weighing 0.8-0.9 kg, were fed a diet containing 200 ppm o-xylene (Bowers et al., 1982). Groups of five animals were killed after 1, 2, 3 and 6 months. The livers were grossly normal, but two types of vesicles were seen with the transmission electron microscope in the hepatocytes of the xylene-treated animals. These vesicles were not present in the control group. The authors noted that the vesicles were involved in the elimination of xylene or its metabolites or both. The purpose of one type of vesicle may have been to increase the surface area of hepatocytes. The occurrence of these vesicles appears to represent an adaptive rather than an adverse effect. The focus of this experiment was exclusively on the liver; no other effects were reported.

Borriston Laboratories, Inc. (1983) performed a 4-week nephrotoxicity screening study with m-xylene in male F-344 rats. Groups of 10 rats received 0.5 or 2.0 g/kg by gavage 5 days/week. There were no adverse effects on the kidney at either treatment level.

NTP (1986) conducted a 13-week gavage study by feeding mixed xylenes (9% o-, 60% m-, 14% p- and 17% ethylbenzene) in corn oil to groups of 10 male and 10 female 6-week-old F344/N rats and to groups of 10 male and 10 female 7-week-old B6C3F1 mice. Five days/week doses of 0 (vehicle control), 62.5, 125, 250, 500 or 1000 mg/kg were administered to rats and 0 (vehicle control), 125, 250, 500, 1000 or 2000 mg/kg were administered to mice. The animals were observed twice daily, body weights were recorded weekly, all animals were subjected to necropsy at termination and vehicle control and high-dose animals were subjected to comprehensive histopathological examination.

All rats survived to termination of treatment. Terminal body weights of high dose (1000 mg/kg) rats were 15% (male) and 8% (females) less than controls. No signs of toxicity were observed and there were no treatment-related gross or histopathological lesions. Two female mice in the high dose (2000 mg/kg) group died during the study. Although cause of death was not determined, gavage error was not ruled out. Neurological signs appeared in mice in the 2000 mg/kg group at 5-10 minutes after dosing and persisted for 15-60 minutes. Body weight gain at 2000 mg/kg was depressed 7% in male mice and 17% in female mice. There were no treatment-related gross or microscopic lesions.

3.1.2. Inhalation. Pertinent subchronic inhalation data for animals exposed to the xylenes are summarized in Table 3-1. For mixed xylenes, Carpenter et al. (1975) reported no adverse effects in rats or dogs exposed to $\leq$3500 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. A comprehensive histopathological examination was performed. Fabre et al. (1960), however, reported bone marrow hyperplasia and glomerulonephritis in rats and rabbits exposed to 3000 mg/m^3, 8 hours/day, 6 days/week for 110-130 days. The latter study, however, was available only from a secondary source and was not available for critical evaluation. Savolainen et al. (1979a) reported altered brain biochemistry and decreased behavioral activity in rats exposed to 1300 mg/m^3, 6 hours/day, 5 days/week for $\leq$18 weeks. The lowest concentration tested in the Carpenter et al. (1975) 13-week study, 770 mg/m^3, 6 hours/day, 5 days/week, appears to be a NOEL for mixed xylenes in rats and dogs.

For o-xylene, Tatrai et al. (1981) observed increased food and water consumption, decreased body weight gain and mild effects on the liver in male rats exposed to 4750 mg/m^3, 8 hours/day, 7 days/week for 1 year.

TABLE 3-1

Subchronic Inhalation Exposure to Xylene

Compound	Species/Strain	Sex/No.	Exposure	Effect	Reference
Mixed xylenes[a]	rat/Harlan-Wistar	M/25	770, 2000 or 3500 mg/m³ 6 hours/day, 5 days/week for 13 weeks	No treatment-related effects on body weight, hematology, blood chemistry or histology (comprehensive examination)	Carpenter et al., 1975
Mixed xylenes[b]	rat/Wistar	M/20	300 ppm (1300 mg/m³) 6 hours/day, 5 days/week for ≤18 weeks	Altered brain biochemistry, decreased behavioral activity	Savolainen et al., 1979a
Mixed xylenes[c]	rat/NR	NR/9	3 mg/l (3000 mg/m³) 8 hours/day, 6 days/week for 110-130 days	Bone marrow hyperplasia, vascular congestion of several organs, glomerulonephritis	Fabre et al., 1960
Mixed xylenes[c]	rabbit/NR	NR/12	3 mg/l (3000 mg/m³) 8 hours/day, 6 days/week for 110-130 days	Bone marrow hyperplasia, vascular congestion of several organs, glomerulonephritis	Fabre et al., 1960
Mixed xylenes[a]	dog/beagle	M/4	770, 2000 or 3500 mg/m³ 6 hours/day, 5 days/week for 13 weeks	No treatment-related effects on body weight, absolute or relative liver or kidney weight, hematology, blood chemistry, urinalysis, ECG	Carpenter et al., 1975
o-Xylene	rat/CFY	M/NR	4750 mg/m³, 8 hours/day, 7 days/week for 7 year	Increased daily food and water consumption, decreased body weight gain, increased relative liver weight, altered liver enzyme activities and hepatic ultrastructural appearance, no effect on BSP retention, SGOT, SGPT or histopathology	Tatrai et al., 1981
	rat/CFY	M/30	3500 ppm (15,200 mg/m³) 8 hours/day for 6 weeks	Decreased body weight, hepatomegaly, ultrastructural hepatocyte changes	Tatrai and Ungvary, 1980
	rat/Sprague-Dawley or Long-Evans	M,F/12	3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks	3 deaths; no effects on weight gain, hematology or histology (limited examination)	Jenkins et al., 1970
	rat/Sprague-Dawley or Long-Evans	M,F/14	337 mg/m³ continuously for 90 days	1 death; no effects on weight gain, hematology or histology (limited examination)	Jenkins et al., 1970
	guinea pig/ Princeton	M,F/15	3358 mg/m³ 8 hours/day, 5 days/week for 6 weeks	No effect on body weight gain, hematology, histology (limited examination)	Jenkins et al., 1970
	guinea pig/ Princeton	M,F/15	337 mg/m³ continuously for 90 days	No effect on body weight, hematology, histology (limited examination)	Jenkins et al., 1970

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TABLE 3-1 (cont.)

Compound	Species/Strain	Sex/No.	Exposure	Effect	Reference
o-Xylene	dog/beagle	M/2	3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks	Neuromuscular tremors in 1 dog; no effect on body gain, hematology or histology (limited examination)	Jenkins et al., 1970
	dog/beagle	M/2	337 mg/m³ continuously for 90 days	No effect on weight gain, hematology or histology (limited examination)	Jenkins et al., 1970
	squirrel monkey/NA	M/2	3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks	No effect on body weight or histology (limited examination)	Jenkins et al., 1970
	squirrel monkey/NA	M/3	337 mg/m³ continuously for 90 days	No effect on body weight or histology (limited examination)	Jenkins et al., 1970
m-Xylene	guinea pig/NR	NR/≥3	300 ppm (1300 mg/m³) 4 hours/day, 6 days/week for 11 weeks	Pulmonary inflammation, mild liver degeneration	Smyth and Smyth, 1928
	guinea pig/NR	NR/≥3	300 ppm (1300 mg/m³) 4 hours/day, 6 days/week for 10 weeks	Chronic catarrhal pulmonary inflammation, renal tubular degeneration	Smyth and Smyth, 1928

[a]8% o-, 65% m-, 8% p-xylene and 19% ethylbenzene

[b]85% m-, 15% other isomers

[c]Benzene-free mixture of unspecified isomers of xylene

NA = Not applicable; NR = not reported

Although the group size was not mentioned, statistical analyses were performed. No mortality was reported. Jenkins et al. (1970) exposed rats, guinea pigs, dogs and monkeys to 3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks or to 337 mg/m³ continuously for 90 days. There were no effects on body weight gain, hematology or histopathological appearance of a limited number of tissues. One (of two) dogs exposed to 3358 mg/m³ had neuromuscular tremors throughout the experiment. Among the rats, 3/12 exposed to 3358 mg/m³ died and 1/14 exposed to 337 mg/m³ died. Cause of death was not reported.

Only one subchronic inhalation study was located for m-xylene. In experiments with guinea pigs exposed to 1300 mg/m³, 4 hours/day, 6 days/week for 10-11 weeks, Smyth and Smyth (1928) reported pulmonary inflammation and liver and kidney degeneration.

Several short-term studies with xylenes in humans, reviewed by U.S. EPA (1986a), suggest that mildly adverse effects may be observed at or near the ACGIH (1986a,b) TWA-TLV of 100 ppm (435 mg/m³) for mixed xylenes or the individual isomers. Hake et al. (1981) exposed groups of male volunteers to p-xylene at 20, 100 or 150 ppm (87, 435 or 651 mg/m³) for 1, 3 or 7.5 hours/day for 5 consecutive days at each exposure level. Males were sedentary except for those exposed for 7.5 hours/day, who exercised for 11 minutes of day 4 of each exposure week. Groups of females were exposed at rest to 100 ppm for 1, 3 or 7.5 hours/day for 5 consecutive days. There were no effects on hematology, urinalysis, EEG, VER, pulmonary ventilation volume, heart rate, metabolic rate, blood pressure or results in various cognitive or performance tests in either men or women, with the exception of two of four men exposed to 150 ppm for 7.5 hours who had decreased performance in the Flanagan coordination test. Nose and throat irritation and headaches were reported in females exposed at 100 ppm for 7.5 hours/day.

Gamberale et al. (1978) exposed male subjects at rest to mixed xylenes (54.4, 12.8, 12.1 and 20.7%, m-, p-, o-xylene and ethylbenzene) at 0, 435 or 1300 mg/m³ for 70 minutes. In a second experiment, eight men were exposed to 1300 mg/m³ for 70 minutes; exercise was added to the first 30 minutes of exposure. In both experiments, five neurological performance tests (addition, simple and choice reaction times, short-term memory and critical flicker fusion frequency) were administered during the last 35 minutes of exposure. There were no effects on the performance tests in the first experiment at either 435 or 1300 mg/m³. In the second experiment, exercise that was associated with increased uptake of xylenes at 1300 mg/m³ resulted in decreased performance in all five tests.

Several studies associate exposure to m-xylene with impaired neurological performance. Savolainen et al. (1979b) noted adverse effects on reaction time and equilibrium in male students exposed to 4.1 µmol/ℓ (435 mg/m³), 6 hours/day for 5 consecutive days for 2 weeks. Tolerance to m-xylene appeared to develop during the first 5 days of the exposure. Savolainen et al. (1984) associated alterations in body balance and simple visual reaction times in healthy males with exercise and exposures to 8.2 µmol/ℓ (870 mg/m³) fluctuating as high as 16.4 µmol/ℓ (1740 mg/m³). Exposures were for 4 hours; some of the subjects exercised for 10 minutes. In other reports from this laboratory with exposure to m-xylene ranging from 90-400 ppm by various schedules for up to 6 weeks, alterations in body balance were noted (Savolainen et al., 1980, 1982a,b; Savolainen, 1980; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979).

3.2. CHRONIC

3.2.1. Oral. NTP (1986) performed a 103-week chronic toxicity carcinogenicity gavage study where mixed xylenes (60.2% m-, 9.1% o-, 13.6% p-xylene

and 17.0% ethylbenzene) in corn oil were administered to 50 male and 50 female F344/N rats at 0 (vehicle control), 250 or 500 mg/kg and to 50 male and 50 female B6C3F1 mice at 0 (vehicle control), 500 or 1000 mg/kg, 5 days/week. High-dose male rats had body weights 5-8% less than controls starting at week 59. A dose-related increase in mortality was also observed in male rats, which became statistically significant at the high dose by week 103. Although some of the deaths were attributed to gavage error, it was possible that the treated rats more forcefully resisted intubation, which indicated a treatment-related behavioral change. The only effect observed in mice was a 5- to 30-minute period of hyperactivity in both sexes in the high-dose group after dosing. No treatment-related histopathological lesions were observed in rats or mice.

3.2.2. Inhalation. U.S. EPA (1986a) reviewed several occupational studies of workers exposed to xylene. Generally, exposure was to a mixture of solvents or exposures were not sufficiently quantified for use in risk assessment. These studies loosely associate exposure to solvents with renal effects (Mikulski et al., 1972; Askergren, 1981, 1982; Askergren et al., 1981a,b; Franchini et al., 1983), liver effects (Kurppa and Husman, 1982; Dossing et al., 1983), ocular and neurophysiological effects (Kurppa and Husman, 1982) and effects on immunocompetency and hematopoiesis (Sukhanova et al., 1969; Moszychzynski, 1981, 1982; Moszychzynski and Lisiewicz, 1983, 1984).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Gavage treatment with mixed xylenes (60.2, 13.6, 9.1 and 17.0% m-, p-, o-xylene and ethylbenzene) at 3100 or 4130 mg/kg/day on days 6-15 of gestation was lethal to pregnant CD-1 mice and produced a mortality incidence of 12/38 at 3100 mg/kg/day and of 15/15 at 4130 mg/kg/day (Marks

et al., 1982). Doses of 2060 and 2580 mg/kg/day caused increased maternal liver weight, increased resorptions and fetal malformations, and decreased fetal body weights (Marks et al., 1982). Doses of 1030 and 520 mg/kg/day had no apparent effects on fetal or maternal toxicity.

In an experiment with individual xylene isomers, Nawrot and Staples (1981) treated pregnant mice with doses of ~780, 1960 or 2610 mg/kg/day on days 6-15 of gestation. Maternal toxicity, increased fetal resorptions and cleft palate were observed with o- and p-xylene at 1960 and 2610 mg/kg/day, but not at 780 mg/kg/day. No cleft palate or maternal toxicity were noted with m-xylene at any dose. In a second experiment in this series, all xylene isomers were given at 2610 mg/kg/day on days 12-15 of gestation and resulted in increased prenatal deaths; the m- and p-isomers resulted in cleft palates. In further testing with m-xylene alone, a significant increase in cleft palates was observed at 2610 mg/kg/day during gestation days 6-15.

3.3.2. Inhalation. Shigeta et al. (1983) reported that IRC mice exposed to 500, 1000, 2000 or 4000 ppm (2174, 4342, 8684 or 17,369 mg/m^3) xylene [isomer(s) not specified] for 6 hours/day on days 6-12 of gestation did not differ from controls in the number of implantation sites or the number of resorbed, dead or externally malformed fetuses. At dose levels of 2000 and 4000 ppm, fetal weights were decreased and delayed skeletal ossification and supranumerary ribs were observed. In neonates from dams allowed to deliver (~1/3 of each group), decreased body weight gain and delayed body hair and tooth development at 4000 ppm were attributed to xylene exposure.

Continuous exposure of 20 pregnant CFY rats to 1000 mg/m^3 mixed xylenes (10% o-xylene, 50% m-xylene, 20% p-xylene, 20% ethylbenzene) on days 9-14 of gestation resulted in an increased incidence of fused sternebrae and

extra ribs in the offspring. The incidence of retarded skeletal development appeared higher but was not significantly different (Hudak and Ungvary, 1978). There was no effect on maternal weight gain, mean litter size, mean placental weight, mean fetal weight, fetal resorption, fetal mortality or visceral malformations.

Pregnant CFY rats were exposed to 150, 1500 or 3000 mg/m³ of each of the isomers of xylene continuously on days 7-14 of gestation (Ungvary et al., 1980). The number of rats in each exposed group was 20 except for the 3000 mg/m³ m-xylene group which contained 30 rats. Groups of 15, 25 or 20 rats served as controls for the o-, m- and p-isomers, respectively. Signs of maternal toxicity included decreased food consumption in all 3000 mg/m³ groups and in the 1500 mg/m³ o-xylene-exposed group. The group exposed to 3000 mg/m³ m-xylene exhibited increased mortality (4/30). The authors stated that maternal weight gain decreased as a function of exposure concentration during the early days of exposure (specific data not provided). The only significant effect on weight gain by day 21 of gestation was in the 3000 mg/m³ m-xylene group. An increase in maternal liver-to-body weight ratio was reported for all o-xylene-exposed groups. Dams exposed to p-xylene at all dose levels had significantly lower placental weights.

Litters from dams exposed to p-xylene at 3000 mg/m³ showed significantly increased fetal loss (69 vs. 4% in controls). The number of pregnant rats was decreased at 3000 mg/m³ o-xylene or m-xylene. The average number of implants per rat was decreased in the group exposed to 3000 mg/m³ m-xylene.

Mean fetal weight was significantly reduced following exposure to all three isomers at the 3000 mg/m³ concentration. Additionally, exposure to o-xylene at 1500 mg/m³ resulted in significant fetal weight reductions.

There were no indications of increased incidence of external, soft tissue or skeletal malformations. An increase in the incidence of extra ribs, classified by the authors as a skeletal anomaly, was seen in litters from dams exposed to 3000 mg/m³ of either m-xylene or p-xylene. Skeletal retardation occurred in fetuses from dams exposed to 3000 mg/m³ o-xylene and in all p-xylene-exposed groups.

In addition, the number of alkaline phosphatase positive proximal convoluted tubules as well as the number and intensity of the positive staining nephrons for succinic dehydrogenase, acid phosphatase and glucose-6-phosphatase was reduced in the o- and p-xylene fetuses from dams exposed to 3000 mg/m³. In the liver and thymus cells from fetuses of dams exposed to all three isomers at 3000 mg/m³ there was a decrease in succinic dehydrogenase and glucose-6-phosphatase activities. The enzyme changes in the kidneys were interpreted by the authors as an indication of a delay in maturation.

Exposure to 1500 mg/m³ produced no adverse effects on litters exposed to m-xylene; 150 mg/m³ produced no adverse effects on litters exposed to o-xylene; and p-xylene resulted in fetotoxicity as evident by delays in skeletal ossification following exposure to the lowest concentration tested (150 mg/m³).

Charles River CD female rats were exposed to mixed xylenes (11% o-xylene, 52% m-xylene, 0.31% p-xylene, 36.1% ethylbenzene) at concentrations of 0, 433 and 1733 mg/m³ on days 6-15 of gestation for 6 hours/day (Litton Bionetics, 1978). There were 25 pregnant dams per exposure group. Animals were sacrificed on day 20 of gestation. The number of implantation sites, resorption sites, live and dead fetuses, fetal weights and external abnormalities were recorded. One-third of the fetuses from each litter were examined for soft-tissue anomalies; the remaining fetuses were examined for

skeletal abnormalities. There was no evidence of maternal toxicity. The only effect apparent was a significant increase in the number of offspring with "unusual skeletal variations." Incidences in fetuses were 19 in the control, 24 in the low-dose group and 37 in the high-dose group; however, the number of litters affected were 9, 6 and 10. The authors did not judge this effect to be treatment-related because the majority of the affected fetuses were from three litters and because all fetuses from these litters were "small."

Delayed skeletal development, supranumerary ribs and increased post-implantation loss were reported in rats exposed to an unspecified mixture of xylene isomers at 230, 1900 or 3360 mg/m³ continuously on days 7-14 of gestation (Balogh et al., 1982). There was no evidence of maternal toxicity.

Mirkova et al. (1983) exposed groups of mated Wistar rats to a commercial mixture of xylene isomers (levels of individual isomers not stated) at 0, 10, 50 or 500 mg/m³, 6 hours/day, 5 days/week during the entire gestation period. At ≥50 mg/m³ postimplantation, loss was increased, fetal body weights were decreased and increased incidences of fetal hemorrhages were noted. High incidences of fetal hemorrhages, however, were noted in all groups including controls. An increased incidence of internal anomalies was reported at 500 mg/m³ and an increased incidence of defects in skeletal ossification was reported at 50 and 500 mg/m³, but the data were not provided for evaluation. In rats allowed to deliver, reduced body weight and "functional inferiority" of several organs were reported in pups from the 50 and 500 mg/m³ groups.

Bio/Dynamics, Inc. (1982) performed an extensive reproduction-developmental toxicity study with a xylene mixture (20.42% o-, 44.2% m-, 20.3% p-xylenes, 12.8% ethylbenzene and 2.4% toluene). Concentrations of 60, 250

or 500 ppm (261, 1086 or 2171 mg/m³), 6 hours/day were provided to groups of 10-20 male and 20-40 female CD rats for 131 days before mating and during a 20-day mating period (both sexes), and during days 1-20 of gestation and days 5-20 of lactation (females). A control group of 30 males and 60 females were sham-exposed. After mating, five treated males were necropsied; the remaining five males were killed after a 3-week recovery period. Female F_0 rats were necropsied and histopathological examinations were performed at weaning of their offspring on lactation day 21. Offspring were sacrificed for necropsy and histopathology at weaning (1/sex/litter) or at postpartum day 49. In a second part of the study, additional groups of males and females were exposed as described and the females were sacrificed on gestation day 21 to evaluate developmental toxicity. In a third part of the study, males and females exposed to 500 ppm as described above were mated to untreated rats.

There were no treatment-related effects on parental mortality, food consumption, body weight gain or appearance at necropsy. No treatment-related effects were observed on mating, fertility or pregnancy indices, gestation length, parturition data, litter size or pup survival. In the developmental toxicity study, a slight but significant decrease was observed in the body weight of female fetuses and delayed fetal skeletal ossification was observed in both sexes from F_0 rats exposed to 500 ppm. There was no increase in the incidence of malformations in pups from treated parents. In the reproduction part of the study, pup weights were reduced at 500 ppm on postpartum day 21. Ovarian weights were reduced in female pups at 250 and 500 ppm sacrificed at day 21 but not at the day-49 sacrifice, and there were no effects on necropsy or histopathology of the pups of either sex at postpartum day 21 or 49.

3.4. TOXICANT INTERACTIONS

The interaction of xylene with ethanol (Savolainen et al., 1978; Elovaara et al., 1980; Savolainen and Riihimaki, 1981; Seppalainen et al., 1981; Riihimaki et al., 1982a,b), 1,1,1-trichloroethane (Savolainen et al., 1982b) and carbon tetrachloride (Tatrai et al., 1979) has been studied. In rats, oral ingestion of alcohol (15% of drinking fluid) potentiates the effect of inhalation exposure to 300 ppm xylene given 6 hours/day, 5 days/week (Savolainen et al., 1978; Elovaara et al., 1980). After 2 weeks of simultaneous exposure, changes in hepatic and renal enzyme activities (7-ethoxycoumarin, o-deethylase, UDP-glucuronosyltransferase and cytochrome P-450) were noted. After 18 weeks of exposure, increased numbers of intracellular lipid droplets were present in the livers of rats exposed to both xylene and ethanol, but were absent from the livers of rats exposed to xylene or ethanol separately. In humans, alcohol ingestion (0.8 g/kg), in conjunction with xylene exposure (290 ppm for 4 hours), increased the effect of alcohol on central equilibrium control mechanisms (Savolainen and Riihimaki, 1981). Xylene doubled the volume of centrilobular liver necrosis caused by ingestion of 2 mℓ/kg bw of carbon tetrachloride in rats (Tatrai et al., 1979). Xylene and 1,1,1-trichloroethane each depressed the metabolism of the other in humans, but no histopathological effects were described (Savolainen et al., 1982b).

4. CARCINOGENICITY

4.1. HUMAN DATA

McMichael et al. (1975) performed a case-control study that associated occupational exposure to organic solvents with a statistically significantly increased incidence of leukemia. No attempt, however, was made to estimate the relative risk associated with specific solvents. In a subsequent analysis of data from the same company studied by McMichael et al. (1975), Arp et al. (1983) indicated that coal-based xylene was the primary component of the solvent mixture to which workers were exposed, but that other (unspecified) solvents were also present.

4.2. BIOASSAYS

4.2.1. Oral. In an NTP (1986) chronic toxicity-carcinogenicity study with mixed xylenes (see Section 3.2.1.), rats were treated with gavage doses of 250 or 500 mg/kg and mice with 500 or 1000 mg/kg, 5 days/week for 103 weeks. NTP (1986) concluded that there was no evidence for the carcinogenicity of mixed xylenes in rats or mice in this experiment.

NTP (1986) reviewed a study in which Sprague-Dawley rats were treated by gavage with xylenes (not otherwise specified) in olive oil at 0 or 500 mg/kg, 4 or 5 days/week for 104 weeks (Maltoni et al., 1985). Observation continued until week 141 at which time survivors were killed for examination. The number of male and female rats having malignant tumors was 11/50 and 10/50 for controls and 14/40 and 22/40 in the treated groups. NTP (1986) stated that because of lack of information on survival and specific tumor types, the study is difficult to interpret.

4.2.2. Inhalation. Tatrai et al. (1981) exposed rats to o-xylene at 4750 mg/m^3, 8 hours/day, 7 days/week for 1 year to investigate effects on the liver (see Section 3.1.2.). No tumors were reported, and this study was inadequate for evaluation of carcinogenicity.

4.3. OTHER RELEVANT DATA

m-Xylene, p-xylene and o-xylene were not mutagenic in several strains of Salmonella typhimurium in the presence or absence of the rat liver microsomal fraction (Florin et al., 1980; Bos et al., 1981; Haworth et al., 1983). Mixed xylenes were not mutagenic in Escherichia coli strains WP2, WP2uvrA, CM611, WP67, WP100, W3110 and p3478 (McCarroll et al., 1981). Xylene was not mutagenic in the Drosophila recessive lethal test (Donner et al., 1980), and did not increase chromosomal aberrations in hematopoietic cells (Donner et al., 1980) or SCEs in human lymphocytes in vitro (Gerner-Smidt and Friedrich, 1978).

4.4. WEIGHT OF EVIDENCE

Relevant animal data regarding the carcinogenicity of the xylenes include the NTP (1986) gavage study, which was an adequate study that was negative in rats and mice, and the Maltoni et al. (1985) gavage study, which suggested a carcinogenic response in rats. In a recent qualitative evaluation, U.S. EPA (1986a) considered the animal data to be inadequate for assessing the carcinogenicity of xylenes. Human occupational data (McMichael et al., 1975; Arp et al., 1983), although these data suggest an association of exposure to xylene with leukemia, are confounded by simultaneous exposure to other solvents and are also inadequate for assessing the carcinogenicity of xylenes. Using the CAG guidelines for cancer risk assessment (U.S. EPA, 1986b), U.S. EPA (1986a) assigned xylenes to Group D -- not classifiable as to human carcinogenicity. This classification is adopted in this analysis for mixed xylenes and the individual (o-, m-, p-) xylene isomers.

8. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1986a,b) recommends a TWA-TLV of 100 ppm (435 mg/m³) and a STEL-TLV of 150 ppm (655 mg/m³) for xylene CAS No. 1330-20-7, which is the mixture of isomers, and also for the individual o-, m- and p-isomers. NIOSH (1975) recommends a 10-minute ceiling of 200 ppm xylene because the attention, judgment and perception of the worker can be altered by the depressant effect of xylene on the CNS. OSHA (1985) has an occupational standard PEL of 100 ppm (435 mg/m³) xylene.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSES (RfD_S)

6.1.1. Oral (RfD_{SO}). Bowers et al. (1982) examined the effects of o-xylene at 200 ppm in the diet for ≤6 months on the livers of rats and Borriston Laboratories, Inc. (1983) examined the effects of m-xylene at 0.5 and 2.0 g/kg, 5 days/week for 4 weeks on the kidneys of rats. Adverse effects were not reported in either study. Although these studies investigated effects in key organs, they are considered too limited in scope to serve as the basis for quantitative risk assessment.

In more comprehensive studies sponsored by NTP (1986), male and female rats were treated by gavage with mixed xylenes at 0, 62.5, 125, 250, 500 or 1000 mg/kg, 5 days/week for 13 weeks, and mice were treated by an identical protocol with 0, 125, 250, 500, 1000 or 2000 mg/kg. The only effect reported in rats was reduced terminal body weight, 15% in males and 8% in females, at 1000 mg/kg. The next lower dosage, 500 mg/kg (357 mg/kg/day when expanded to daily treatment) represents a NOEL in rats in this experiment. Adverse effects in mice included transient neurological signs (immediately after dosing) and reduced body weight gain. In addition, two females at this dosage died, but the cause of death was not determined.

Xylenes at relatively high dosages have been associated with developmental toxicity in laboratory animals. Marks et al. (1982) administered mixed xylenes to pregnant mice at dosages of 520-4130 mg/kg/day on days 6-15 of gestation. Doses of 3100 and 4130 mg/kg/day were associated with fetal deaths, while doses of 2060 and 2580 mg/kg/day were associated with mild maternal toxicity (increased liver weight) and developmental toxicity. Neither maternal nor developmental toxicity occurred at the two lowest doses, 520 and 1030 mg/kg/day. In another developmental toxicity study,

Nawrot and Staples (1981) treated pregnant mice with the individual o-, m- and p-isomers of xylenes at ~780, 1960 or 2610 mg/kg/day on days 6-15 of gestation, at 2610 mg/kg/day on days 12-15 of gestation and in further trials with m-xylene at 2610 mg/kg/day on gestation days 6-15. Although the results were not reported clearly in the secondary source from which these data were taken, it appears that all isomers were associated with prenatal death and an increased incidence of cleft palate, which was generally accompanied by maternal toxicity. The lowest dosage tested, 780 mg/kg/day, appears to be a NOAEL for fetotoxicity for all three xylene isomers.

The NOAELs for developmental toxicity, 1030 mg/kg/day for mixed xylenes (Marks et al., 1982) and 780 mg/kg/day for the individual isomers (Nawrot and Staples, 1981), are sufficiently above the NOEL of 357 mg/kg/day for subchronic toxicity in rats that the latter may serve as the basis for an RfD_{SO}. Application of an uncertainty factor of 100, 10 for interspecies extrapolation and 10 to protect unusually sensitive individuals, results in an RfD_{SO} of 4 mg/kg/day, or 250 mg/day for a 70 kg human. These values are considered provisional for mixed xylenes and individual isomers, pending the results of subchronic testing of individual isomers (OSW) and mixed xylenes (OTS) in progress (U.S. EPA, 1986a).

6.1.2. Inhalation (RfD_{SI}). The subchronic animal inhalation studies with xylenes (see Table 3-1), do not clearly define thresholds of toxicity for mixed xylenes or any of the individual isomers. For mixed xylenes, Carpenter et al. (1975) reported no adverse effects in rats or dogs exposed to $\leq$3500 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. In contrast, however, Fabre et al. (1960) reported several lesions including glomerulonephritis in rats exposed to 3000 mg/m^3, 8 hours/day, 6 days/week for 110-130 days, and Savolainen et al. (1979a) reported decreased behavioral

activity in rats exposed to 1300 mg/m³, 6 hours/day, 5 days/week for ≤18 weeks. A NOAEL for behavior effects was not identified.

In an experiment with o-xylene in rats, 4750 mg/m³, 6 hours/day, 5 days/week for 1 year was associated with decreased body weight gain and increased relative liver weight, but with no effects on biochemical indicators of liver damage or on histopathology of unspecified organs (Tatrai et al., 1981). Jenkins et al. (1970) exposed rats, guinea pigs, dogs and monkeys to 3358 mg/m³, 8 hours/day, 5 days/week for 6 weeks or to 337 mg/m³ continuously for 90 days. No effects on weight gain, hematology or a limited histological examination were observed. Unexplained deaths occurred in both treated groups of rats.

Smyth and Smyth (1928) observed pulmonary inflammation and liver or kidney degeneration (or both) in guinea pigs exposed to 1300 mg/m³ m-xylene, 4 hours/day, 6 days/week for 10-11 weeks

The most comprehensive inhalation study was a reproductive toxicity experiment in which rats were exposed to mixed xylenes at 0, 60, 250 or 500 ppm (0, 261, 1086 or 2171 mg/m³), 6 hours/day for ~190 days before mating and during mating, gestation and lactation (Bio/Dynamics, Inc., 1982) (see Section 3.3.2.). There were no effects on parameters of subchronic toxicity in parental rats. Signs of fetal toxicity, which were limited to the 500 ppm group, included delayed skeletal ossification in both sexes and reduced body weights of female fetuses. Reduced pup weights on lactation day 21, which indicates reproductive toxicity, were also observed in this group. Reduced ovarian weights of female pups were observed at 250 and 500 ppm on day 21 but not on day 49. This appeared to be a transient nonadverse effect. This experiment, therefore, appears to define a LOAEL for rats of 500 ppm for 6 hours/day that is associated with fetotoxicity and impaired

neonatal growth, and a NOAEL of 250 ppm for 6 hours/day that is associated with transient reduction in ovarian weights in offspring.

With the exception of the unexplained death of one rat in a group of 14 exposed to o-xylene at 337 mg/m³ continuously for 90 days (Jenkins et al., 1970), none of the subchronic animal studies reviewed in Section 3.1.2. define adverse effects below the NOAEL of 250 ppm (1086 mg/m³) for 6 hours/day in the Bio/Dynamics, Inc. (1982) study. Other inhalation developmental toxicity studies, however, suggest that adverse effects may occur at or below the NOAEL in the Bio/Dynamics, Inc. (1982) study. Hudak and Ungvary (1978) observed an increased incidence of fused sternebrae and extra ribs in offspring of rats exposed to mixed xylenes at 1000 mg/m³ continuously on days 9-14 of gestation. Balogh et al. (1982) reported delayed skeletal development, extra ribs and increased postimplantation loss in rats exposed to an unspecified mixture of xylenes at ≥230 mg/m³ continuously on days 7-14 of gestation, but data were not sufficient for evaluation. Mirkova et al. (1983) reported defects in skeletal ossification and "functional inferiority" of several organs of pups from rats exposed to a commercial mixture of xylene isomers at ≥50 mg/m³ but not at 10 mg/m³, 6 hours/day, 5 days/week. Ungvary et al. (1980) exposed pregnant rats to the individual isomers of xylene at 150, 1500 or 3000 mg/m³ continuously on days 7-14 of gestation. Adverse fetal effects were noted with m-xylene at 3000 mg/m³ but not at 1500 mg/m³, with o-xylene at ≥1500 mg/m³ but not at 150 mg/m³ and with p-xylene at all exposure levels.

Benchmarks of toxicity and transformed doses from studies (all in rats) that are sufficient for quantitative risk assessment are presented in Table 6-1. The Bio/Dynamics, Inc. (1982) NOAEL for mixed xylenes of 250 ppm or 181 mg/kg/day appears to be challenged by a LOAEL of 5.7 mg/kg/day that is

TABLE 6-1

Subchronic and Developmental Toxicity in Rats

Compound	Exposure	Transformed Dose (mg/kg/day)	Effect	Benchmark	Reference
Mixed xylenes	500 ppm (2171 mg/m³) 6 hours/day for ~190 days	362[a]	fetotoxicity	LOAEL	Bio/Dynamics, Inc., 1982
	250 ppm (1086 mg/m³) 6 hours/day for ~190 days	181[a]	no subchronic toxicity or adverse developmental effects	NOAEL	Bio/Dynamics, Inc., 1982
	50 mg/m³, 6 hours/day, 5 days/week throughout gestation	5.7[b]	fetotoxicity	LOAEL	Mirkova et al., 1983
	10 mg/m³, 6 hours/day, 5 days/week throughout gestation	1.1[b]	no adverse effects	NOAEL	Mirkova et al., 1983
o-Xylene	1500 mg/m³ continuously on gestation days 7-14	956[b]	fetotoxicity	LOAEL	Ungvary et al., 1980
	150 mg/m³ continuously on gestation days 7-14	95.6[b]	no adverse effects	NOAEL	Ungvary et al., 1980
m-Xylene	3000 mg/m³ continuously on gestation days 7-14	1911[b]	fetotoxicity	LOAEL	Ungvary et al., 1980
	1500 mg/m³ continuously on gestation days 7-14	956[b]	no adverse effects	NOAEL	Ungvary et al., 1980
p-Xylene	150 mg/m³ continuously on gestation days 7-14	95.6[b]	fetotoxicity	NA[c]	Ungvary et al., 1980

[a]Calculated by expanding to continuous exposure and estimating an inhalation rate for rats using the U.S. EPA (1980) expression [0.105 (body weight/0.113)$^{0.7}$], where body weight of 0.300 kg was estimated from data provided by investigators.

[b]Calculated as described in footnote a except that a reference body weight for rats of 0.35 kg was used.

[c]A NOAEL for fetotoxicity of p-xylene was not identified.

NA = Not applicable

estimated from the Mirkova et al. (1983) study. The nature of the xylene mixture used in the Mirkova et al. (1983) study, however, was not described and incidence data for internal anomalies was not presented. Furthermore, the incidence of fetal hemorrhage was high in all groups including controls, which suggests that the health of the rats or the conduct of the experiment was compromised. Therefore, the Mirkova et al. (1983) study, in light of the more comprehensive and more thoroughly reported Bio/Dynamics, Inc. (1982) study, is not considered further in risk assessment.

The developmental toxicity study by Ungvary et al. (1980) with different xylene isomers indicates a similarity in inhalation toxicity between the o- and m-isomers, but a markedly greater toxicity for p-xylene. The study defines fetotoxicity NOAELs for the o- and m-isomers but fails to define a NOAEL for p-xylene.

Using the 181 mg/kg/day NOAEL for mixed isomers, the Bio/Dynamics, Inc. (1982) study can be used to approximate a NOAEL for p-xylene. The 18 mg/kg/day NOAEL dose identified for mixed xylenes contain ~20.3% or 36.7 mg/kg/day p-xylene, a dose that may be considered a NOAEL for p-xylene. This estimation for a NOAEL for p-xylene indicates that an RfD based on a dose of ~36.7 mg/kg/day should be applicable to mixed xylenes and to the individual isomers. The level of 36.7 mg/kg/day is not used as the basis of the RfD because short-term experiments in humans with m-xylene (Savolainen et al., 1980, 1982a,b; Savolainen, 1980; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979) and with p-xylene (Hake et al., 1981) suggest that impaired neurological performance in humans may be a more sensitive endpoint of xylene toxicity than endpoints evaluated in animals and that the human data may be a more appropriate basis for an RfD_I. Therefore, the

RfD_I of 0.3 mg/m³ for a 70 kg human that is derived in Section 6.2.2., is adopted as the RfD_{SI} for mixed xylenes and the individual isomers for the purpose of this document.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Chronic oral toxicity data are restricted to the 103-week NTP (1986) gavage study of mixed xylenes in which rats were treated with 0, 250 or 500 mg/kg and mice with 0, 500 or 1000 mg/kg, 5 days/week. High-dose mice of both sexes experienced a transient period of hyperactivity immediately after dosing. High-dose male rats had body weights 5-8% less than controls starting at week 59 and statistically significantly increased mortality at the end of the study. No effects were observed at 250 mg/kg, which is a NOEL in this experiment. An RfD_0 can be derived from the NOEL of 250 mg/kg in this study. Multiplication by 5/7 to expand dosage over 7 days/week and application of an uncertainty factor of 100, 10 to extrapolate from rats to humans and 10 to protect unusually sensitive individuals, results in an RfD_0 of 2 mg/kg/day or 126 mg/day for a 70 kg human. This value, which agrees with that derived by U.S. EPA (1986a), is adopted as a provisional RfD_0 for mixed xylenes and the individual isomers of xylene pending results of the subchronic oral testing (see Section 6.1.1.). It is expected to be protective against developmental toxicity as discussed in Section 6.1.1.

U.S. EPA (1986a) derived a CS for xylene based on the increased mortality observed in male rats that were treated by gavage with mixed xylenes at 500 mg/kg, 5 days/week for 103 weeks in the NTP (1986) study. The 500 mg/kg dose was transformed to 357 mg/kg/day. Multiplication by the cube root of the ratio of the animal body weight (0.425 kg estimated from data provided) to the reference human body weight (70 kg) resulted in a human equivalent

dose of 65 mg/kg/day or 4550 mg/day for a 70 kg human. The human MED of 4550 mg/day is equivalent to an RV_d of 1. An RV_e of 10 was chosen for the effect of increased mortality. Multiplying the RV_d by the RV_e results in a CS of 10. This CS is adopted for mixed xylenes and the individual xylene isomers.

6.2.2. Inhalation (RfD_I). Animal inhalation data for the xylenes were restricted to subchronic and developmental toxicity studies, which were evaluated for risk assessment in Section 6.1.2. A NOAEL of 181 mg/kg/day for mixed xylenes and an approximate NOAEL of 36.7 mg/kg/day for p-xylene were identified in a subchronic toxicity-reproduction rat study (Bio/Dynamics, Inc., 1982). The ACGIH (1986a,b) TWA-TLV of 100 ppm (435 mg/m³) has been in effect since 1967 and is regarded as protective against irritation, narcosis and chronic injury. Recent human studies (Hake et al., 1981; Savolainen et al., 1980, 1982a,b; Savolainen, 1980; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979), however, associated mild neurophysiological disorders with exposure at or near the TLV. Recently, the U.S. EPA (1989) RfD Workgroup considered the CNS effects of the Hake et al. (1981) study for the derivation of an RfD_I. It was highly unusual that an acute human study was used for the derivation of the RfD_I; however, the RfD Workgroup recognized that this study is supported by other human studies (even with their limitations). Based on the CNS effects, the 100 ppm dose was a LOAEL and the 20 ppm dose was a NOAEL. The 20 ppm (87 mg/m³) was adjusted to 27 mg/m³ as the human equivalent concentration. By applying an uncertainty factor of 100 (10 for intraspecies variability and an additional factor of 10 to compensate for the use of a 5-day study) to this NOEL, an RfD of 0.3 mg/m³ was derived and verified by the RfD Workgroup on May 18, 1989.

6.3. CARCINOGENIC POTENCY (q_1* or Unit Risk Slope)

Negative results in the oral NTP (1986) cancer study with mixed xylenes in rats and mice and no tumors reported in the 1-year inhalation study with o-xylene in rats (Tatrai et al., 1981) preclude estimation of carcinogenic potencies for oral or inhalation exposure to xylene.

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APPENDIX

Summary Table for Xylene

	Species	Experimental Exposure/Dose	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} (formerly AIS)					
o-, m-, p- and mixed xylenes	human	100 ppm (434 mg/m³) adjusted to 136 mg/m³	slight neurophysiological impairment		Savolainen et al., 1980, 1982a,b; Savolainen, 1980; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979; Hake et al., 1981
		20 ppm (87 mg/m³) adjusted to 27 mg/m³ human equivalent concentration	NOAEL	0.3 mg/m³	
RfD_I (formerly AIC)					
o-, m-, p- and mixed xylenes	human	100 ppm (434 mg/m³) adjusted to 136 mg/m³	slight neurophysiological impairment		Savolainen et al., 1980, 1982a,b; Savolainen, 1980; Riihimaki and Savolainen, 1980; Savolainen and Linnavuo, 1979; Hake et al., 1981
		20 ppm (87 mg/m³) adjusted to 27 mg/m³ human equivalent concentration	NOAEL	0.3 mg/m³	
Oral					
RfD_{SO}					
o-, m-, p- and mixed xylenes	rat	500 mg/kg, 5 days/week for 13 weeks (357 mg/kg/day)	NOEL	250 mg/day	NTP, 1986
RfD_O					
o-, m-, p- and mixed xylenes	rat	250 mg/kg, 5 days/week for 103 weeks (180 mg/kg/day)	NOEL	126 mg/day	NTP, 1986
Maximum CS					
o-, m-, p- and mixed xylenes	rat	500 mg/kg, 5 days/week for 103 weeks (357 mg/kg/day) (MED = 4550 mg/kg/day, RV_d = 1)	mortality (RV_e = 10)	CS = 10	NTP, 1986